Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-23, 41, 47, 69 and 95-99 are pending in the application. Claim 70 is sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 95-99 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Support for the new claims.

Support for new claims 95-99 is provided by at least original claims 1, 21, 41, 47, 67 and 70.

II. Claim Rejections - 35 USC § 112

At page 3 of the Office Action mailed June 20, 2001, the Examiner rejected claims 1-23, 41, 47, 69, and 70 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Specifically, the Examiner rejected claim 1 because it was "drawn to a tripartite leader (TPL) sequence [that] encodes first, second, or third, different TPL exons" and it was "unclear what is meant to be different about the exons." The Examiner asked "[a]re the exons derived from TPL exons from different adenoviruses?"

One of skill in the art would understand that the meaning of "different" is "not the same." Therefore, "different" as used in the claims means that the TPL exons may be from different adenoviruses or alternatively be from the same adenovirus as long as they are not the same TPLs.

The Examiner next indicated that the recitation "intron" in claim 4 and "promoter" in claim 6 lacked antecedent basis. Claim 4 has been amended to depend on claim 2. Therefore, there is now antecedent basis for "intron."

Concerning claim 6, the appropriate antecedent basis is already present in claim 6 for "said" promoter. The first reference to "promoter" recites "further comprising *a* promoter." The next reference to "said" promoter refers back to the first recitation of "promoter."

The Examiner next states that "Claim 11 is [*sic*] recites a 'vector complementing plasmid'.. ." and it is unclear what this is. Applicants respectfully draw the Examiner's attention to the specification beginning at page 19, line 18 that recites:

> *Complementing Plasmid*: This term is generally used herein to describe plasmid vectors used to deliver particular nucleotide sequences into a packaging cell line, with the intent of having said sequences stably integrate into the cellular genome.

Thus, in claim 11 an "adenovirus vector complementing plasmid" is a plasmid that contains sequences intended to complement sequences deleted in the adenovirus vector.

The Examiner indicated that claim 17 recited the limitation "chimeric" in line 1 and that there was an insufficient antecedent basis for this limitation in the claim. Applicants have amended claim 17 to depend on claim 16, thereby providing appropriate antecedent basis.

Beginning in the last paragraph of page 3 of the Office Action, the Examiner alleged that claim 22 is vague and confusing as to what the adenovirus vector genome actually comprises. Applicants disagree. Specifically, the Examiner stated that:

> Claim 22 states that the cell line produces one protein, which is denoted as "an" adenovirus protein, but further states that the cell line produces an adenovirus early gene and a fiber gene (emphasis added). Claim 21 indicated that the cell line supports the production of a viral gene, not genes, which is indicated in the second portion of claim 22. Claim 22 further indicates that the cell line produces these genes in order to complement the genes that are deficient in the vector genome. However, none of the preceding claims (1 -20) indicated that the vector genome was deficient in any way. For example, claim 17 is drawn to an adenovirus that "comprises" an Ad3 head domain and an Ad5 tail domain. The claim does not suggest that the adenovirus is missing parts.

Claim 22 which is dependent on claim 21 that is then dependent on claim 12 is drawn to a "packaging cell line" that comprises *inter alia*, the molecule of claim 1 and also complements "an adenovirus early protein gene and a fiber gene." There is nothing in claim 1 or any other claim upon which claim 22 depends that precludes the use of a deficient vector genome requiring complementation by a protein produced in the cell line of claim 22. It is irrelevant that the Examiner argues that "none of the preceding claim (1-20) indicated that the vector genome was deficient in any way." The Examiner's argument inappropriately reads a limitation into the claims upon which claim 22 depends. Therefore, contrary to the Examiner's argument, there is nothing confusing or vague about claim 22.

At page 4, the Examiner states that:

> claim 23 is vague and indefinite because the claim is stating that a singular deficient gene is complemented by the expression of the gene under an inducible promoter and is dependent from Claim 22. Are both the early and the fiber gene under the control of the inducible promoter, or is only one gene under control of that particular kind of promoter?

Claim 23 first refers to "deletion of *said* deficient adenovirus gene." The end of claim 23 recites "*said* gene under the control of an inducible promoter." Therefore, it is clear that *at least* the "deficient gene" is under control of the promoter. There is no limitation, however, in this claim concerning whether either the early protein gene or the fiber gene is under control of the inducible promoter.

In claim 41, the Examiner objected to the phrase "alternatively operatively linked to a promoter." Solely in an attempt to expedite prosecution, Applicants have deleted the recitation "alternatively" from claim 41 and also added new dependent claim 95

The Examiner also stated that

> Claims 41 and 47 are vague and indefinite for depending from claims in a non-elected group. To expedite prosecution, claim 41 is considered as dependent from claim 21 and claim 47 is considered to be dependent from 1. However, applicant is required to amend the claim to correct dependency.

It is not clear to Applicants how the method claims of claim 41 and 47 can be dependent on the non-method claims of claim 21 and 1, as the Examiner suggested. However, Applicants have amended claim 41 and have also added new claims 95-97 in an attempt to address what are believed to be the Examiner's concerns.

The Examiner objected to claim 69 because of its dependency and lack of antecedent basis. Applicants have amended claim 69 to depend from claim 12 rather than claim 9. The Examiner also noted that

> Claim 69 is also unclear because the packaging cell line is selected from specific cell lines and an epithelial cell line (emphasis added). Are there two

> cell lines that are mixed together somehow to form a conglomerate cell line? If "or" is intended in lieu of and, does this mean that that [*sic*] if one chose the other cell lines in the list, such as 293 cells, that cell line does not require the stably integrated nucleic acid molecule, as required by the epithelial cell line?

Applicants have amended the claim to more clearly point out the claimed subject matter.

The Examiner noted that claim 70 recites the limitation "particle" in line 1 and that there was insufficient antecedent basis for this limitation in the claim. It is believed that claim 70 should have been dependent on claim 67 that was part of non-elected restriction group II. Therefore, Applicants have cancelled claim 70 without prejudice or disclaimer and added claims 98-99 in an attempt to address the Examiner's concerns. Concerning the terms "biologically active fragment" and "a tumor-suppressive gene and/or a suicide protein, one of skill in the art would understand these terms.

Based on all of the above, the rejection under 35 U.S.C. §112, second paragraph is either mooted or overcome and should be withdrawn.

II. Rejection of claims 1-4, 6, 7, 9-16, 20-23, 41, 47, and 69 under 35 U.S.C. § 102(a)

At page 6 of the Office Action, the Examiner rejected claims 1-4, 6, 7, 9-16, 20-23, 41, 47, and 69 rejected under 35 U.S.C. 102(a) as allegedly being anticipated by Nemerow *et al.* in WO 98/13499 - hereinafter "the '499 application." Applicants respectfully traverse this rejection.

The Examiner's attention is drawn to the amendment of September 26, 2001 which amends the current application to include the '499 application as part of the priority claim.

Therefore, the '499 application is not prior art, this rejection is overcome and should be withdrawn.

III. Rejection of the claims under 35 U.S.C. § 103(a)

A. Rejection of claims 8 and 17

In the Office Action at page 6, the Examiner rejected claims 8 and 17 under 35 U.S.C. § 103 (a) as allegedly being unpatentable over the '499 application. as applied to claims 1-4, 6, 7, 9-16, 20-23, 41, 47, and 69 above, and further in view of Stevenson *et al.* (*J. Virol. 71*:4782-4790, 1997 - hereinafter "Stevenson"). Applicants respectfully traverse this rejection.

As noted above, the '499 application is now part of the priority claim. Therefore, the '499 application is not prior art and any rejection using the '499 application in combination with other art is overcome and should be withdrawn.

B. Rejection of claim 70.

In the Office Action at page 7 the Examiner rejected claim 70 under 35 U.S.C. §103(a) as allegedly being unpatentable over the '499 application and Stevenson as applied to claims 1-4, 6-17, 20-23, 41, 47, and 69 above, and further in view of Guo *et al.* (*Chin. J. Path. 27*:194-197, 1998). Applicants respectfully traverse this rejection.

As noted above, the '499 application is now part of the priority claim. Therefore, the '499 application is not prior art and any rejection using the '499 application in combination with other art is overcome and should be withdrawn.

III. Allowable Subject Matter

The Examiner noted that claims 5, 18, and 19 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicants thank the Examiner for acknowledging that claims 5, 18 and 19 would be allowable if amended as suggested. Applicants, however, are not currently amending the claims as suggested, because it is believed that once the prior art objections are removed, the independent claims upon which claims 5, 18 and 19 depend will also be allowable.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (202) 371-2589.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Lawrence B. Bugaisky

Lawrence B. Bugaisky
Attorney for Applicants
Registration No. 35,086

Date: December 19, 2001

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

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Version with markings to show changes made

4. (Once Amended) The isolated nucleic acid molecule of claim [1] 2 wherein said intron is native adenovirus intron 1.

17. (Once Amended) The cell line of claim [12] 16 wherein said chimeric protein comprises an Ad3 head domain and an Ad5 tail domain or an Ad5 head domain and an Ad3 tail domain.

41. (Once amended) [The method of claim 38] A method for producing an adenovirus particle comprising:

1) providing a packaging cell line wherein said packaging cell line comprises:

a) a stably integrated first nucleic acid molecule [alternatively] operatively linked to a promoter, and said first nucleic acid is operatively linked to a second nucleic acid molecule encoding an adenovirus structural protein, wherein said first nucleic acid molecule comprises an adenovirus tripartite leader (TPL) nucleotide sequence operatively linked to an intron containing an RNA processing signal, said TPL nucleotide sequence comprising (a) first and second different TPL exons or (b) first, second and third different TPL exons, said TPL exons selected from the group consisting of complete TPL exon 1, partial TPL exon 1, complete TPL exon 2 and complete TPL exon 3 and

b) said cell line supports the production of a recombinant adenovirus vector genome by complementation of a deficient viral gene in said vector genome, and

2) producing said adenovirus particle.

69. (Once amended) The packaging cell line of claim [9] 12 wherein said cell line is selected from the group consisting of 293, A549, W163, HeLa, Vero, 211, 211A and an epithelial cell line [comprising] wherein said cell line comprises [the] said stably integrated nucleic acid molecule.